Proposed Re-evaluation Decision PRVD2016-08

# 4-Aminopyridine

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# Overview

## What Is the Proposed Re-evaluation Decision

After a re-evaluation of the repellent 4-aminopyridine, Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing continued registration of products containing 4-aminopyridine for sale and use in Canada. Interim label amendments for 4-aminopyridine products to limit user and environmental exposure were implemented in 2009 (REV2009-01 Re-evaluation Note, *4-Aminopyridine Mitigation Measures*, 13 January 2009). As a requirement of the continued registration of products containing 4-aminopyridine, further risk reduction measures are proposed as part of this re-evaluation to minimize exposure with respect to human health and the environment.

An evaluation of available scientific information found that products containing 4-aminopyridine do not present unacceptable risks to human health or the environment when used according to label directions. No additional data are being requested at this time. This proposal affects all end-use products containing 4-aminopyridine registered in Canada.

This Proposed Re-evaluation Decision is a consultation document[1] that summarizes the science evaluation for 4-aminopyridine and presents the reasons for the proposed re-evaluation decision.

The information is presented in two parts. The Overview describes the regulatory process and key points of the evaluation, while the Science Evaluation provides detailed technical information on the assessment of 4-aminopyridine.

The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (please see contact information indicated on the cover page of this document).

## What Does Health Canada Consider When Making a Re-evaluation Decision?

The PMRA's pesticide re-evaluation program considers potential risks, as well as value, of pesticide products to ensure they meet modern standards established to protect human health and the environment. 4-Aminopyridine is one of the active ingredients re-evaluated under Re-evaluation Program 1 as per Regulatory Directive DIR2001-03, *Pest Management Regulatory Agency Re-evaluation Program*.

[1] "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

This program relies as much as possible on foreign reviews, typically United States Environmental Protection Agency (USEPA) Reregistration Eligibility Decision (RED) documents. For products to be re-evaluated under Program 1, the foreign review must meet the following conditions:

- it covers the main science areas, such as human health and the environment, that are necessary for Canadian re-evaluation decisions;
- it addresses the active ingredient and the main formulation types registered in Canada; and
- it is relevant to registered Canadian uses.

Given the outcome of foreign reviews and a review of the chemistry of Canadian products, the PMRA will propose a re-evaluation decision and appropriate risk-reduction measures for Canadian uses of an active ingredient. In this decision, the PMRA takes into account the Canadian use pattern and issues (for example, the federal Toxic Substances Management Policy [TSMP]).

Based on the health and environmental risk assessments published in the 2007 RED, the USEPA concluded that 4-aminopyridine was eligible for reregistration provided risk-reduction measures were adopted. The PMRA compared the American and Canadian use patterns and found the USEPA assessments described in this RED were an adequate basis for the proposed Canadian re-evaluation decision.

For more details on the information presented in this overview, please refer to the Science Evaluation section of this consultation document.

## What Is 4-Aminopyridine?

4-Aminopyridine is a repellent that is used for the control of feral pigeons, sparrows, and certain blackbirds and cowbirds, in, on, or in the area of structures, nesting and roosting sites. The products are registered as Restricted class and are for use by, or under the supervision of, government agencies and pest control operators only.

## Health Considerations

### Can Approved Uses of 4-Aminopyridine Affect Human Health?

**4-Aminopyridine is unlikely to affect your health when used according to the proposed label directions.**

Handlers of the restricted products could be exposed to 4-aminopyridine by mixing the treated bait (end-use product) with untreated bird feed or by entering treated sites. The PMRA considers two key factors when assessing health risks: the levels at which no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which exposure is well below levels that cause no effects in animal testing are

considered acceptable for continued registration. In the case of 4-aminopyridine, clinical studies in humans that investigated the efficacy and safety of 4-aminopyridine as a therapeutic agent in spinal cord injury and multiple sclerosis patients were used to establish the dose level to assess risk.

The USEPA concluded that 4-aminopyridine was unlikely to affect human health provided that risk-reduction measures were implemented (e.g., personal protective equipment for handlers, ensuring product placement is in places inaccessible to children and the public, removal of unused product at the end of the day and further instructions for authorized handlers to ensure public safety). These conclusions apply to the Canadian situation, and equivalent risk-reduction measures are currently in place in Canada, with the exception of personal protective equipment for handlers picking up dead birds and unused bait. As part of this re-evaluation, the PMRA is proposing personal protective equipment for handlers picking up dead birds and unused bait (refer to Appendix IV).

## Environmental Considerations

### What Happens When 4-Aminopyridine Is Introduced Into the Environment?

**4-Aminopyridine is unlikely to affect non-target organisms when used according to the current label directions.**

The USEPA concluded that the reregistration of 4-aminopyridine was acceptable provided risk-reduction measures to further protect the environment were implemented (e.g., pre-baiting requirement to ensure that non-target species do not come into contact with treated bait and proper disposal of dead birds). These conclusions apply to the Canadian situation, and equivalent risk-reduction measures are currently in place in Canada. However, to provide further clarity, is it proposed that both the common names and the scientific names of target birds are listed on the end-use product labels to clearly distinguish target species from non-target species.

## Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human health and the environment. These directions must be followed by law. As a result of the re-evaluation of 4-aminopyridine, the PMRA is proposing further risk-reduction measures related to human health and the environment for product labels.

### Human Health

- Personal protective equipment for handlers removing unused bait and dead birds.

**Environment**

- List both the common names and the scientific names of target birds.
- Revise wording with respect to pre-baiting to refer to "non-target bird species" rather than "desirable or protected bird species".

## What Additional Scientific Information is Required?

No additional data are required.

## Next Steps

Before making a final re-evaluation decision on 4-aminopyridine, the PMRA will consider all comments received from the public in response to this consultation document. A science-based approach will be applied in making a final decision on 4-aminopyridine. The PMRA will then publish a Re-evaluation Decision[2] that will include the decision, the reasons for it, a summary of comments received on the proposed decision and the PMRA's response to these comments.

[2] "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

# Science Evaluation

## 1.0 Introduction

4-Aminopyridine is a repellent, which acts by blocking potassium ion channels in nerve fibres.

The PMRA used assessments of 4-aminopyridine from the United States Environmental Protection Agency (USEPA). The USEPA Reregistration Eligibility Decision (RED) document for 4-aminopyridine, dated September 27, 2007, as well as other information on the regulatory status of 4-aminopyridine in the United States can be found at www.regulations.gov (Docket ID EPA-HQ-OPP-2007-0400).

## 2.0 Use Description of 4-Aminopyridine

4-Aminopyridine is registered in Canada as a pesticide for the control of feral pigeons, sparrows, and certain blackbirds and cowbirds, in, on, or in the area of structures, nesting and roosting sites. 4-Aminopyridine is formulated as an impregnated choice bird food (corn chops, whole corn or mixed grains). The products are registered as Restricted class and are for use by, or under the supervision of, government agencies and pest control operators only. The product is diluted with untreated bird food and applied by hand, using chemical-resistant gloves, at an application rate ranging from 0.259 g a.i. to 1 g a.i. per treatment area (i.e., 0.5 to 2 kilograms of blended bait, depending on the product and dilution ratio used, to be applied in selected sites throughout the feeding area).

The American and Canadian use patterns were compared. The end-use products in the United States have the same formulation (mixed grains, corn chops and whole corn), and either the same guarantee (0.5% active ingredient) or a higher guarantee (1% active ingredient). The application rate in Canada is encompassed by that of the United States. The United States use pattern is more extensive than that of Canada, having the same registered use sites, in addition to feedlots and having the same target pests as Canada, in addition to grackles, starlings and crows. Based on this comparison of use patterns, it was concluded that the USEPA RED for 4-aminopyridine is an adequate basis for the re-evaluation of uses of 4-aminopyridine in Canada.

All current uses are being supported by the registrant and were, therefore, considered in the re-evaluation of 4-aminopyridine. Appendix I lists all 4-aminopyridine products that are registered as of 5 January 2016 under the authority of the *Pest Control Products Act*. 4-Aminopyridine is also known as fampridine, the medicinal ingredient of the human drug Fampyra which was approved by Health Canada in 2012[3]. The drug has also been available for years compounded in pharmacies chiefly for use in multiple sclerosis and spinal cord injury.

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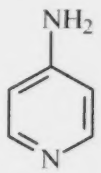
[3] Summary Basis of Decision (SBD) for PrFAMPYRA™, Bureau of Cardiology, Allergy and Neurological Sciences, Health Canada, July 9, 2012.

## 3.0 The Technical Grade Active Ingredient, Its Properties and UsesError! Bookmark not defined.

### 3.1 Identity of the Technical Grade Active Ingredient

| | |
|---|---|
| **Common name** | 4-aminopyridine |
| **Function** | Repellent |
| **Chemical family** | Pyridine |
| **Chemical name** | |
| 1 **International Union of Pure and Applied Chemistry (IUPAC)** | pyridin-4-amine |
| 2 **Chemical Abstracts Service (CAS)** | 4-pyridinamine |
| **CAS Registry Number** | 504-24-5 |
| **Molecular formula** | $C_5H_6N_2$ |
| **Structural formula** |  |
| **Molecular weight** | 94.1 g/mol |
| **Purity of the technical grade active ingredient** | 98.5% |
| **Registration Number** | 30740 |

Based on the manufacturing process used, impurities of human health or environmental concern as identified in the Canada Gazette, Part II, Vol. 142, No. 13, SI/2008-67 (2008-06-25), including TSMP Track 1 substances, are not expected to be present in the product.

### 3.2 Physical and Chemical Properties of the Technical Grade Active Ingredient

| Property | Result | Interpretation |
|---|---|---|
| Vapour pressure at 23°C | 21.9 to 27.9 mPa | High volatility. |
| Ultraviolet/Visible absorption spectrum | Not expected to absorb at $\lambda \geq 300$ nm | Phototransformation is unlikely. |
| Solubility in water at 25°C | 111 - 112 g/L | Very soluble in water. |
| *n*-Octanol–water partition coefficient (*K*ow) at 23±2°C | Log $K_{ow}$ = - 0.7 to - 0.9 | Bioaccumulation is unlikely. |
| Dissociation constant | $pK_a$ = 10.21 | Mobility in soil increases as soil pH increases. |

## 4.0 Human Health

Toxicology studies in laboratory animals describe potential health effects resulting from various levels of exposure to a chemical and identify dose levels at which no effects are observed. Unless there is evidence to the contrary, it is assumed that effects observed in animals are relevant to humans and that humans are more sensitive to effects of a chemical than the most sensitive animal species. The USEPA RED for 4-aminopyridine used human systemic toxicity studies in addition to animal studies. These studies were primarily focused on the efficacy of this active when used as a therapeutic agent.

Exposure to 4-aminopyridine may occur while loading/applying (i.e., mixing treated bait with untreated bait and placing the bait in the desired location) or by entering treated sites to remove unused bait and/or dead birds. When assessing health risks, the PMRA considers two key factors: the levels at which no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers).

In their 2007 RED, the USEPA concluded that the end-use products formulated with 4-aminopyridine met the safety standard under the American *Federal Insecticide, Fungicide and Rodenticide Act* and would not pose unreasonable risks or adverse effects to humans and the environment if used according to the amended product labels.

## 4.1 Toxicological Summary

4-aminopyridine is a central nervous system toxicant. It is highly acutely toxic to mammals via the oral (dog $LD_{50}$ = 3.7 mg/kg; rat $LD_{50}$ = 20 mg/kg), dermal (rabbit $LD_{50}$ = 327 mg/kg) and inhalation ($LD_{50}$ = 0.53 mg/L) routes of exposure. Four oral subchronic toxicity studies, two in rats and two in dogs, were determined to be unacceptable for quantitative evaluation but provided useful qualitative information. The acute and subchronic toxicological effects of 4-aminopyridine are manifested as hyperexcitability, hyperirritability, salivation, tremors, and muscular incoordination.

The USEPA used the available animal studies together with clinical human data along with an accidental 4-aminopyridine human poisoning report for purposes of their risk assessment. The USEPA's use of human studies for 4-aminopyridine were in accordance with the USEPAs Final Rule promulgated on January 26, 2006, related to Protections for Subjects in Human Research, which is codified in 40 CFR Part 26. Three human clinical studies were available that investigated the efficacy and safety of 4-aminopyridine in spinal cord injury and multiple sclerosis patients. Adverse effects in humans ingesting low levels of 4-aminopyridine (5-30 mg/day)[4] were nervousness, giddiness or dizziness, memory alteration, cramps, arterial vasospasm and peripheral paraesthesia. A higher dose in an accidental poisoning case (one-time estimated dose of 60 mg) produced additional effects including weakness, intense diaphoresis, feeling of impending doom, dyspnea, agitation and combative behaviour, and profound thirst. Human studies demonstrated that 4-aminopyridine is eliminated quickly from the body and effects did not accumulate with continuous exposure.

The USEPA's toxicological endpoints for assessing risk to human health are summarized in Appendix II. The point of departure and uncertainty factors employed by the US EPA in their assessment are applicable to the Canadian situation. For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. The currently restricted end-use products containing 4-aminopyridine are not intended for use on food/feed crops and consequently, dietary exposure to this active ingredient is not expected. Based on the use pattern, residential exposure is also not expected. Therefore, the *PCPA* factor[5] is not applicable for 4-aminopyridine risk assessment at this time[6].

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4 Where 5 mg/day equates to 0.07 mg/kg bw/day of 4-aminopyridine, the LOAEL selected for the point of departure.

5 Science Policy Note, SPN2008-01, The Application of Uncertainty Factors and the *Pest Control Product Act* Factor in the Human Health Risk Assessment of Pesticides. Health Canada's Pest Management Regulatory Agency, 29 July 2008.

6 Based on the information available in the public domain with respect to the use of 4-aminopyridine as a therapeutic agent (Product monograph, FAMPYRA™, Fampridine, 10 mg Sustained Release Tablet, Potassium Channel Blocker, Biogen Idec Canada Inc, November 26, 2014), there is no concern for developmental or reproductive toxicity. Consequently, no pre- or post-natal concerns were identified that would warrant the application of an additional factor for occupational risk assessments.

### 4.2 Occupational Exposure

Occupational risk is estimated by comparing potential exposures with the most relevant endpoint from toxicology studies being used to calculate a margin of exposure (MOE). This is compared to a target MOE incorporating uncertainty factors protective of the most sensitive subpopulation. If the calculated MOE is less than the target MOE, it does not necessarily mean that exposure will result in adverse effects, but mitigation measures to reduce risk would be required.

Workers can be exposed to 4-aminoyridine when loading (i.e., combining treated bait with untreated bait), applying the pesticide (i.e., placing the treated bait in the desired location) and when conducting activities such as removing unused bait and dead birds.

#### 4.2.1 Handler Exposure and Risk

The USEPA did not identify any intermediate or long-term occupational dermal or inhalation endpoints of concern. Therefore, they did not assess the occupational risk for these routes of exposure.

Short-term dermal and inhalation handler exposure analyses were performed using surrogate unit exposure data from ExpoSAC Policy Number 14 that addressed seed treatment scenarios (liquid formulation), assuming baseline personal protective equipment (PPE) (long-sleeved shirt, long pants, shoes, and socks) plus gloves. The two exposure scenarios considered were (1) Load/apply pre-treated baits and (2) Multiple activities (representative of mixing the treated bait with untreated bait and application of the blended bait as well as picking up dead birds and unused bait).

Short-term dermal and inhalation risk was based on handling 454 g a.i. per day, a lowest observed adverse effect level (LOAEL) of 0.07 mg/kg bw/day, a target margin of exposure (MOE) of 30 and a default body weight for an adult handler of 70 kg. The target MOE is based on a 10X uncertainty factor for potential variation in sensitivity among members of the human population (intraspecies) and a 3X uncertainty factor for the use of a LOAEL to extrapolate a NOAEL.

The USEPA reported acceptable short-term combined dermal and inhalation MOEs of 210 for loading and applying and 120 for multiple activities. Both MOEs were based on a commercial seed treatment scenario. The following mitigation measures were required by the USEPA:

> All loaders and applicators (application includes activities such as picking up dead birds and unused bait), and other handlers must wear: a long-sleeved shirt and long pants, shoes plus socks, and chemical-resistant gloves.

The RED adequately addressed exposure scenarios associated with the uses of products containing 4-aminopyridine in Canada, and conclusions derived from the RED apply to the Canadian situation. The wearing of a long sleeved shirt, long pants and chemical resistant gloves for loading and applying the product, are currently in place on all registered Canadian end-use products and were previously implemented as per Re-evaluation Note (REV2009-01). However, these personal protective equipment should also be implemented for those handlers picking up dead birds and unused bait. Refer to Appendix IV for the proposed revision to the label statement.

### 4.2.2 Postapplication Exposure and Risk

The US EPA did not assess occupational postapplication risks to workers because no potential postapplication exposure scenarios were identified. This is considered applicable to the Canadian situation and no mitigation measures with respect to postapplication exposure are proposed.

## 4.3 Non-Occupational Exposure

### 4.3.1 Residential Exposure and Risk

Since all 4-aminopyridine products are restricted use products, no residential handler exposure will occur. Post-application residential exposures to 4-aminopyridine are not expected to occur because Canadian labels instruct applicators to place treated bait in areas that are inaccessible to the public. Furthermore, in areas open to the public, baiting is to be performed at elevated sites where feasible. Where baiting at elevated sites is not feasible and ground baiting is required, a certified applicator or someone under his/her direct supervision must ensure children do not come into contact with the bait during the entire application period. Authorized handlers must not leave the site until all dead or dying birds and unused bait are retrieved from the site.

The USEPA did conduct an incidental oral ingestion exposure assessment based on a child accidentally eating one piece of treated bait (corn), a daily exposure of 3.8 mg a.i. (per seed) (based on a 1% formulation and the assumption that there are 1200 seeds in 454 grams of corn) and the assumption the child weighs 15 kg. The calculated MOE of 0.3 was below the target MOE of 30 and thus of concern to the USEPA. As a result, the USEPA required label statements to be added to all end-use product labels in order to mitigate potential for exposure to children (i.e., (1) do not apply treated bait in areas accessible to children; (2) in populated areas and areas open to the public perform baiting at elevated sites; (3) where baiting at elevated sites is not feasible, a certified applicator or authorized handler must ensure children do not come in contact with the blend and the authorized handler must not leave the site until all dead/dying birds and unused bait are retrieved from the site; and (4) product must not be stored or even temporarily placed in locations accessible to children).

No residential uses are registered in Canada. However, the above risk reduction measures to reduce potential for exposure to children and the general public is present on all current Canadian end-use product labels and no further mitigation measures with respect to residential exposure are proposed.

### 4.3.2 Dietary Exposure and Risk

There are no food uses of 4-aminopyridine registered in the United States and drinking water exposure was not expected by the USEPA based on the following:

- Small volume of 4-aminopyridine used (less than 113 kg/year) in the United States was expected to limit widespread contamination of surface source drinking water;
- 4-aminopyridine must be used in areas above ground, such as elevated bait stations, where possible and;
- Applicators must pick up and remove any remaining product at the end of the dosing period.

No food uses of 4-aminopyridine are registered in Canada. According to current labels, baiting must be performed at elevated areas where feasible. Where ground baiting is required, a certified applicator or someone under his/her direct supervision must ensure that non-target species do not come in contact with the bait during the entire baiting application period and the handler must not leave the site until all dead or dying birds and unused bait are retrieved from the site. These risk reduction measures minimize contamination, or residues of 4-aminopyridine, in food (i.e. meat, milk, poultry, or eggs) or water. Based on this, no further mitigation measures are proposed with respect to food and drinking water exposure.

## 4.4 Aggregate Exposure and Risk Assessment

Aggregate risk combines the different routes of exposure to 4-aminopyridine. Acute and chronic aggregate risk assessments are comprised of contributions from food and drinking water exposures. Short- and intermediate-term aggregate risk assessments are comprised of contributions from food, drinking water and non-occupational exposure (dermal, inhalation).

With the exception of potential accidental ingestion exposure, no residential exposures were expected. Also, dietary exposures from food and drinking water were not expected. Therefore, no aggregate risk assessment was conducted by the USEPA.

Based on the similarity of use patterns between Canada and the United States, the USEPA aggregate exposure conclusions are considered applicable to the uses of 4-aminopyridine in Canada. No mitigation measures are proposed with respect to aggregate risk.

## 4.5 Cumulative Exposure and Risk

The *Pest Control Products Act* requires that the PMRA consider the cumulative exposure to pesticides with common mechanisms of toxicity. For the current re-evaluation, the PMRA did not identify information indicating that 4-aminopyridine shares a common mechanism of toxicity with other pest control products, nor is this active ingredient considered to produce a metabolite common to other active ingredients. Therefore there is no requirement for a cumulative assessment at this time.

## 5.0 Environment

### 5.1 Environmental Fate

Based on its high water solubility, low octanol/water partition co-efficient, and low soil/water distribution coefficient value estimated with structure activity relationship modeling, the USEPA expected 4-aminopyridine to be mobile in the environment. The high aqueous solubility along with the low octanol/water partition coefficient suggested that 4-aminpyridine has a low potential to accumulate in the fatty tissues of fish. Since abiotic half-life values could not be derived from submitted data, the USEPA assumed 4-aminopyridine to be stable for both hydrolysis and photolysis for the purposes of exposure modelling. Based on modelling (EPI Suite (v3.12) PCKOCWIN (v1.6)), the USEPA estimated that under aerobic conditions the biotic half-life ranged between 3 and 32 months and under anaerobic conditions 4-aminopyridine was stable. It was therefore assumed that 4-aminopyridine would be persistent in the environment.

### 5.2 Environmental Exposure and Risk Assessment

The USEPA did not conduct a quantitative ecological risk assessment. Instead, a qualitative risk description was developed by considering label information, use patterns, fate and ecotoxicity data, models and other information to assist in framing the potential risk to non-target aquatic and terrestrial organisms. Gross estimates of the oral dose of bait needed to reach the $LD_{50}$ for the most sensitive bird and mammal were calculated by the USEPA by utilizing the percent active ingredient per weight of the bait, the recommended dilution rates of treated bait with untreated bait, the reported $LD_{50}$s for birds and mammals (red winged blackbird $LD_{50}$ 2.4 mg/kg bw; rat $LD_{50}$ 28.7 mg/kg bw; dog $LD_{50}$ = 3.7 mg/kg bw) and assumed mean body weights for each of the surrogate species (assumed mean body weights were 0.07 kg blackbird, 0.40 kg rat and 10 kg dog). The results were expressed as weight in milligrams of bait that could be consumed per surrogate bird or mammal to reach their respective $LD_{50}$ (0.168 mg/blackbird, 11.5 mg/rat and 37 mg/dog). The amount of active ingredient per seed was also estimated for canary seed, rape seed, wheat, sorghum, chopped corn and whole corn. The milligrams of active ingredient per seed values were used by the USEPA to estimate the number of seeds that would have to be consumed to reach the $LD_{50}$ for each surrogate species.

It was determined that it took very few seeds to reach the $LD_{50}$ level for birds. For small and large mammals significantly more seeds would need to be ingested. However, when expressed as total grams of bait, the USEPA determined that the amounts would be within the capability for mammals to consume in a short period of time. Thus it was determined that there was an acute risk to birds and mammals from potential 4-aminopyridine exposure. Chronic risks to birds and mammals were considered to be minimal because it would be more likely that the amount of 4-aminopyridine consumed would result in quick mortality. In addition, 4-aminopyridine is designed to repel birds, thus reducing the probability of chronic exposure. Incident data from the USEPA Ecological Incident Information system (121 incidents involving non-target birds from 1971 to 2005) also indicated that many birds can potentially be killed from a single exposure event (i.e., acute risk).

Impacts of 4-aminopyridine to terrestrial plants were not expected because it was found to have no effect on germination of corn up to 1 ppm and no effect on fresh weights of seedlings up to 10 ppm following a single application. Furthermore it is applied as treated bait and generally used in either heavily managed areas and/or areas densely populated by humans.

Based on concerns for potential acute risks to non-target birds and mammals, the USEPA required the following mitigation measures to be included on all end-use product labels to reduce ecological exposure:

- Requirement that a certified applicator or someone under his/her direct supervision ensures that non-target species do not come in contact with the blend during the entire application period. That authorized handler must stay on the site during the entire application period (from the time the 4-aminopyridine treated bait is placed in the application site to the time treated bait and any dead or dying birds are removed). The authorized handler must ensure that children, pets, and non-target species do not come in contact with the blend.

- Birds killed during treatment must be disposed of by burial or incineration.

- Prebaiting target birds. Prebaiting promotes feeding by target species and provides an opportunity to assess potential exposure to non-target species. Application of 4-aminopyridine treated bait to be prohibited if non-target species are observed feeding on the pre-bait.

- Both the common names and the scientific names of target birds must be listed on the label to clearly distinguish target species from non-target species.

Based on the similarity of use patterns between Canada and the United States, the USEPA conclusions with respect to the environment are considered applicable to the uses of 4-aminopyridine in Canada. Equivalent risk-reduction measures are currently in place on all registered Canadian end-use products, with the exception of the scientific names of target birds. To provide further clarity, it is proposed that both the common names and the scientific names of target birds be listed on the end-use product labels to clearly distinguish target species from non-target species. In addition, it is proposed that the wording on the Canadian labels with respect to pre-baiting be revised to refer to "non-target bird species" rather than "desirable or protected bird species". Refer to Appendix IV for the proposed revisions to the label.

## 6.0 Value

4-aminopyridine is a repellent used to manage populations of sparrows, certain blackbirds, cowbirds and feral pigeons on structures. The control of birds is necessary for several reasons including unsightliness of bird droppings, damage to structures, contamination of food and feed, spread of disease, and source of allergens.

## 7.0 Pest Control Product Policy Considerations

### 7.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances (those that meet all four criteria outlined in the policy, in other words, persistent [in air, soil, water and/or sediment], bioaccumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*).

During the re-evaluation process, 4-aminopyridine was assessed in accordance with the PMRA Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*, and evaluated against the Track 1 criteria. PMRA has reached the following conclusion:

- The repellent 4-aminopyridine does not meet Track 1 criteria, and is not considered a Track 1 substance. See Appendix III for comparison with Track 1 criteria.

### 7.2 Contaminants and Formulants of Health or Environmental Concern

Contaminants in the technical[7] were compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*.[8] The list is used as described in the PMRA Notice of Intent NOI2005-01 and is based on existing policies and regulations including: DIR99-03; and DIR2006-02, and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusion:

- Technical grade 4-aminopyridine does not contain any impurities of human health or environmental concern as identified in the *Canada Gazette*.

## 8.0 Incident reports

Since 26 April 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA. Information on the reporting of incidents can be found on the Pesticides and Pest Management portion of Health Canada's website.

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7 PMRA Document Number 2242575. Evaluation Report for Category B.1.1,B.1.3 Application. This Evaluation Report can be found in the public registry on the PMRA website.

8 *Canada Gazette*, Part II, Volume 139, Number 24, pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

Available information from the PMRA database, as of 5 January 2016, indicates three environment incident reports were submitted related to 4-aminopyridine. The first incident involved the death of 40 grackles, a type of songbird, in Quebec City in 2009. The PMRA has concluded that it was highly probable that the ingestion of Avitrol caused the grackle mortality and it was determined that Avitrol was not used according to label directions. The other two incident reports were classified as minor in severity.

There were no human or domestic animal incidents involving 4-aminopyridine in the PMRA database.

## 9.0 Organization for Economic Co-operation and Development Status of 4-Aminopyridine

Canada is part of the Organisation for Economic Co-operation and Development (OECD), which groups member countries and provides a forum in which governments can work together to share experiences and seek solutions to common problems.

As part of the re-evaluation of an active ingredient, the PMRA takes into consideration recent developments and new information on the status of an active ingredient in other jurisdictions, including OECD member countries. In particular, decisions by an OECD member country to prohibit all uses of an active ingredient for health or environmental reasons are considered for relevance to the Canadian situation.

4-Aminopyridine is currently acceptable for use in other OECD countries, including the United States and Australia for use as a repellent. It is also registered for use in Australia as a veterinary drug and for use in other OECD countries, including the EU as a human drug. As of 10 August 2015, no decision by an OECD member country to prohibit all uses of 4-aminopyridine for health or environmental reasons has been identified.

## 10.0 Proposed Re-evaluation Decision

The PMRA is proposing that products containing 4-aminopyridine are acceptable for continued registration with the implementation of the proposed risk-reduction measures. The proposed mitigation measures are presented in Appendix IV. No additional data are being requested at this time.

## 11.0 Supporting Documentation

PMRA documents, such as Regulatory Directive DIR2001-03, *Pest Management Regulatory Agency Re-evaluation Program*, and DACO tables (datacode tables) can be found on the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra. PMRA documents are also available through the Pest Management Information Service. Phone: 1-800-267-6315 within Canada or 1-613-736-3799 outside Canada (long distance charges apply); fax: 613-736-3798; e-mail: pmra.infoserv@hc-sc.gc.ca.

The federal TSMP is available through the Environment Canada website.

The USEPA RED document for 4-aminopyridine is available at www.regulations.gov (Docket ID EPA-HQ-OPP-2007-0400).

## List of Abbreviations

| | |
|---|---|
| a.i. | active ingredient |
| bw | body weight |
| CAS | Chemical Abstracts Service |
| DACO | data code |
| g | gram(s) |
| ha | hectare |
| IUPAC | International Union of Pure and Applied Chemistry |
| kg | kilogram(s) |
| $K_{ow}$ | *n*-octanol–water partition coefficient |
| L | litre(s) |
| $LD_{50}$ | lethal dose to 50% |
| LOAEL | lowest observed adverse effect level |
| m | metre(s) |
| mg | milligram(s) |
| MOE | margin of exposure |
| NOAEL | no observed adverse effect level |
| OECD | Organisation for Economic Co-operation and Development |
| PCPA | *Pest Control Products Act* |
| pH | -log10 hydrogen ion concentration |
| PIC | Prior Informed Concent |
| PMRA | Pest Management Regulatory Agency |
| PPE | personal protective equipment |
| PRVD | Proposed Re-evaluation Decision |
| RED | Reregistration Eligibility Decision |
| RVD | Re-evaluation Decision |
| TGAI | technical grade active ingredient |
| TSMP | Toxic Substances Management Policy |
| USEPA | United States Environmental Protection Agency |

# Appendix I Registered Products Containing 4-Aminopyralid as of 5 January 2016

| Registration Number | Marketing Class | Registrant | Product Name | Formulation Type | Guarantee (%) |
|---|---|---|---|---|---|
| 12095 | Restricted | Avitrol Corporation | Avitrol Corn Chops | particulate | 0.5 |
| 12096 | Restricted | Avitrol Corporation | Avitrol Whole Corn | particulate | 0.5 |
| 12098 | Restricted | Avitrol Corporation | Avitrol Mixed Grains | particulate | 0.5 |
| 30740 | Technical | Avitrol Corporation | 4-aminopyridine | solid | 98.5 |

# Appendix II Toxicological Endpoints for 4-Aminopyralid Health Risk Assessments

| Exposure Scenario | Dose (mg/kg bw/day) | Study | Target UF/SF or MOE [a] |
|---|---|---|---|
| Incidental oral, dermal, and inhalation.<br>Short-term<br>(1–30 days) | LOAEL = 0.07 mg/kg/day based on mild adverse effects of paresthesias/ dysesthesias, dizziness/light-headedness, gait instability, nausea/ vomiting, restlessness/ anxiety | Based on three clinical human studies (spinal cord injury and multiple sclerosis patients) | MOE = 30<br><br>$UF_A$ = 1x (interspecies)<br>$UF_H$ = 10x (intraspecies)<br>$UF_L$ = 3x (use of LOAEL to extrapolate NOAEL) |
| Cancer (oral, dermal, inhalation) | Classification: There is no animal carcinogenicity data or human data to evaluate the carcinogenic potential of 4-aminopyridine. For this reason, the USEPA RED has maintained a classification of not classifiable as to human carcinogenicity. | | |

a UF refers to total of uncertainty factor. MOE refers to desired margin of exposure for occupational exposure assessments.

# Appendix III Toxic Substances Management Policy Considerations - Comparison to TSMP Track 1 Criteria

| TSMP Track 1 Criteria | TSMP Track 1 Criterion Value | | Are Criteria Met for 4-Aminopyridine? |
|---|---|---|---|
| CEPA toxic or CEPA toxic equivalent[1] | Yes | | Yes |
| Predominantly anthropogenic[2] | Yes | | Yes |
| Persistence[3] | Soil | Half-life ≥ 182 days | 3 to 32 months (based on modelling by the USEPA: EPI Suite (v3.12) PCKOCWIN (v1.6)) |
| | Water | Half-life ≥ 182 days | |
| | Sediment | Half-life ≥ 365 days | |
| | Air | Half-life ≥ 2 days or evidence of long-range transport | The vapour pressure ($2.09 \times 10^{-4}$ mm Hg) and Henry's Law Constant ($2.4 \times 10^{-9}$ atm – $m^3$/ mole) indicate that there is some potential for 4-aminopyridine to volatilise. |
| Bioaccumulation[4] | Log $K_{ow} \geq 5$ | | No: -0.7 to -0.9 |
| | BCF ≥ 5000 | | Not available. |
| | BAF ≥ 5000 | | Not available. |
| Is the chemical a TSMP Track 1 substance (all four criteria must be met)? | | | No, does not meet TSMP Track 1 criteria. |

[1]All pesticides will be considered CEPA-toxic or CEPA-toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (all other TSMP criteria are met).

[2]The policy considers a substance "predominantly anthropogenic" if, based on expert judgment, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.

[3]If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air), then the criterion for persistence is considered to be met.

[4]The log *K*ow and/or BCF and/or BAF are preferred over log $K_{ow}$.

# Appendix IV Proposed Label Amendments for Products Containing 4-Aminopyridine

The label amendments presented below do not include all label requirements for individual end-use products, such as first aid statements, disposal statements, precautionary statements and supplementary protective equipment. Information on labels of currently registered products should not be removed unless it contradicts the label statements provided below.

I) Under **PRECAUTIONS**, following statements are proposed to be removed:

"Wear a long-sleeved shirt, long pants, shoes plus socks, and chemical-resistant gloves during loading and applying this product"

And replace with the following statement:

"Wear a long-sleeved shirt, long pants, shoes plus socks, and chemical-resistant gloves during loading and applying this product as well as during picking up dead birds and unused bait."

II) All species targeted by the end-use product are proposed to be stated on the label. The common and scientific names of each targeted species are proposed to be included on the label.

III) Under DIRECTIONS FOR USE, the following statement is proposed to be revised as follows:

"Careful observation of bird habits should be made to establish proper feeding locations and to determine that no desirable or protected bird species are present that may feed on [product]."

To read:

"Careful observation of bird habits should be made to establish proper feeding locations and to determine that no non-target bird species are present that may feed on [product]."

## References

**Studies/Information Considered in the Chemistry Assessment**

**A. LIST OF STUDIES/INFORMATION SUBMITTED BY REGISTRANT**

| PMRA Document Number | Reference |
|---|---|
| 1992016 | 1968, Technical Data Sheet: Phillips Avitrol 200 (1861), DACO: 2.14,2.14.1,2.14.3,2.3,2.3.1,2.4,2.5,4.2.1,4.2.9,9.6.2,9.6.2.3,9.6.3 CBI |
| 1992025 | 1969, 4-AP Data Sheet: Properties of 4AP, DACO: 2.12,2.13.2,2.14.1,2.14.2,2.14.3,2.14.4,2.14.7,2.14.8,2.7,8.2,8.2.1 CBI |
| 1992032 | 1970, Identity, Physical & Chemical Properties, and Formulations of Avitrol., DACO:2.11,2.11.1,2.11.2,2.11.3,2.12,2.13.2,2.14,2.14.1,2.14.13,2.14.14,2.14.2,2.14.3,2.14.4,2.7,2.8,2.9 CBI |
| 1992030 | 1980, Administrative Record of the Registration Standard for 4-Aminopyridine (Avitrol), DACO: 2.11.4, 2.12, 2.12.1, 2.13.4, 2.14, 2.14.1, 2.14.13, 2.14.14, 2.14.2, 2.14.4, 2.14.7, 2.14.8, 2.7, 2.8, 2.9, 4.2, 4.2.1, 4.2.2, 4.2.3, 4.2.4, 4.2.5, 4.2.6, 4.3, 4.3.1, 4.3.2, 4.3.3, 4.3.4, 4.3.5, 4.3.6, 4.3.7, 4.3.8, 4.4, 4.4.1, 4.4.2, 4.4.3, 4.4.4, 4.4.5, 4.5, 4.5.1, 4.5.10, 4.5.11, 4.5.12, 4.5.13, 4.5.14, 4.5.2, 4.5.3, 4.5.4, 4.5.5, 4.5.6, 4.5.7, 4.5.8, 4.5.9, 8.1, 8.2, 8.2.1, 8.2.2, 8.2.2.1, 8.2.2.2, 8.2.2.3, 8.2.2.4, 8.2.3.2, 8.2.3.4, 8.2.3.4.2, 8.2.3.5.2, 8.2.4.2, 8.5, 8.5.1, 8.6, 9.5.1, 9.5.2, 9.5.2.1, 9.5.2.2, 9.5.2.3, 9.5.3, 9.5.3.1, 9.5.3.2, 9.6, 9.6.1, 9.6.2.3, 9.6.2.6, 9.6.3, 9.6.6, 9.7, 9.8.4 CBI |
| 1992005 | 1987, 4-Aminopyridine:Analysis and Certification of Product Ingredients, DACO: 2.11,2.11.1,2.11.2,2.11.3,2.12,2.12.1,2.13,2.13.1,2.13.2,8.2,8.2.1 CBI |
| 1992024 | 1987, 4-Aminopyridine-Physical & Chemical Characteristics: HLA 6001-170: HLA 6001-197, DACO: 2.12,2.13.2,2.14.1,2.14.10,2.14.11,2.14.12,2.14.13,2.14.14,2.14.2,2.14.3,2.14.4,2.14.6,2.14.7,2.14.8,2.14.9,2.7,2.8,8.2,8.2.1,8.2.2.3,8.2.3.5.2,8.2.4.2 CBI |
| 1992023 | 1988, 4-Aminopyridine-Physical and Chemical Characteristics: HLA 6001-170: HLA 6001-197, DACO: 2.12,2.13.2,2.14,2.14.1,2.14.10,2.14.11,2.14.12,2.14.13,2.14.14,2.14.2,2.14.3,2.14.4,2.14.6,2.14.7,2.14.8,2.14.9,2.7,2.8,8.2,8.2.1,8.2.2.3,8.2.3.5.2,8.2.4.2 CBI |
| 1992017 | 2010, Avitrol Technical Data Sheet, DACO: 2.14,2.14.1,9.6.3 CBI |
| 2147265 | 2011, Preliminary Analysis, DACO: 2.13.1 CBI |
| 2147264 | 2011, Production Process, DACO: 2.11.3 CBI |

| PMRA Document Number | Reference |
|---|---|
| 2156614 | 2012, Preliminary Analysis and Enforcement Analytical Method, DACO: 2.13.1 CBI |
| 2229613 | Additional Certificate of Analysis, DACO: 2.13 CBI |
| 2147267 | Certificate of Analysis, DACO: 2.13 CBI |
| 2147268 | Certificate of Analysis, DACO: 2.13 CBI |
| 2147269 | Certificate of Analysis, DACO: 2.13 CBI |
| 2147270 | Certificate of Analysis, DACO: 2.13 CBI |
| 2147271 | Certificate of Analysis, DACO: 2.13 CBI |
| 2228242 | Confirmation of Intermediate, DACO: 2.11.3 CBI |
| 2228241 | Description of Staring Materials, DACO: 2.11.2 CBI |
| 2147263 | Identification of the Catalyst, DACO: 2.11.2 CBI |
| 2150164 | Manufacturing Process, DACO: 2.11.3 CBI |